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(19)

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(54) VASCULAR PROSTHESES

(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, Imperial Chemical House, Millbank, London SW1P 3JF a British Company do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:

This invention relates to tubular products, particularly to vascular prostheses, and to methods of making these.

Our UK Patent 1 527 592 describes the production of products comprising fibres by the electrostatic spinning of organic materials.

The process of electrostatic spinning involves the introduction of a liquid into an electric field, whereby the liquid is caused to produce fibres which tend to be drawn to an electrode. While being drawn from the liquid the fibres usually harden, which may involve mere cooling (where the liquid is normally solid at room temperature, for example), chemical hardening (for example by treatment with a hardening vapour) or evaporation of solvent (for example by dehydration). The product fibres may be collected on a suitably located and shaped receiver and subsequently stripped from it.

We have found that tubular products obtained by the electrostic spinning method of the aforementioned patent application find particular use as synthetic blood vessels (vascular prostheses) which may be employed for example to replace damaged blood vessels in the mammalian body. Such vascular prostheses typically have at least a tubular portion of internal diameter up to 3 cm.

Accordingly, the invention provides a vascular prosthesis comprising fibres prepared by electrostatically spinning an organic material and formed into a tube by collecting the spun fibres on a suitably shaped mandrel, the prosthesis comprising a tubular portion having a bore of maximum internal cross-sectional dimension up to 3 cm. Preferably the internal diameter will be 0.3 to 3 cm, more preferably 0.5 to 2 cm and still more preferably 0.8 to 1.5 cm.

The vascular prosthesis of the invention will usually be in the form of a simple tube having a bore of circular cross-section and of substantially constant diameter along its length. However, the diameter of the bore may vary, regularly or irregularly, e.g. the bore may taper or it may include constrictions, and/or the cross-sectional appearance of the bore may depart from the circular, for example it may be oval or rectangular or any other shape as may be appropriate. When the bore departs from the circular, the dimensions referred to above will be the maximum dimensions. The exterior of the prosthesis may follow the contour of the bore, or it may be of different configuration.

The prosthesis may comprise reinforcing components which may, for example, be circular, spiral or longitudinal, and may be rigid, elastic, flexible, or partially flexible (e.g. in a predetermined direction). However, it is usually preferred that the material is reinforced, for example by applying to one surface of the product a reinforcing layer, which itself may be electrostatically spun, or by incorporating reinforcement within the wall of the product itself. Thus, electrostatically spun products may be reinforced by incorporating within the wall thereof a web which may be woven or non-woven, or an alternative arrangement of fibres. We particularly prefer to employ as reinforcement a helix of suitable fibre, said helix being located within the walls of a tubular pro-

duct comprising electrostatically spun fibrous material. Although it is usual to enclose the reinforcement within the wall material we do not exclude the possibility of applying it to a surface of the product where its presence will not be disadvantageous. The thickness of reinforcement will be influenced inter alia by the thickness of the wall, the location of the reinforcement and the reinforcement strength required. In general the thickness of the reinforcement will be less than that of the wall, although where the reinforcement lies at a surface of the wall and may project therefrom the thickness of the reinforcement may be thicker than that of the wall. Generally the thickness of the reinforcement (or of reinforcing fibres) will be of the order of 0.1 to 10 times the thickness of the wall, preferably 0.2 to 0.8 times.

Suitable reinforcing materials include metallic, polymeric or glass fibre.

The configuration of the prosthesis will be such that it fulfils the physical requirements of its function, for example it may have a configuration such that its attachment to an adjacent vessel is facilitated, or it may be such that flexure of the vessel is encouraged or restricted in certain directions.

The prostheses according to the present invention may be spun from a solution of or a dispersion of a polymer or its precursors. Polymers which may be conveniently spun from solution include high molecular weight fibre forming polymers; in particular we would mention polyurethane, polyamides and polyacrylonitrile. Polymers which may conveniently be spun from dispersion include polytetrafluoroethylene and polyesters as well as those listed above. As an example of a polymer precursor which may be spun from solution we mention urea formaldehyde which may be cross-linked subsequent to spinning by treatment with acid vapour.

Water soluble polymers, e.g. polyvinyl alcohol, polyvinyl pyrrolidone, and polyethylene oxide, may be spun from aqueous solution. While we do not exclude the possibility that prostheses prepared from such materials may be used as prepared, preferably such prostheses are given at least a degree of insolubility in aqueous medium e.g. by cross-linking with a suitable reagent.

Where the prostheses are spun from a dispersion the spinning material comprises preferably also a solution of an additional component which acts to enhance the viscosity of the suspension and to improve its fibre forming properties. Most convenient for this purpose, we have found, is an additional organic component which subsequent to fibre formation, can, if desired, be destroyed during sintering. The use of such an additional organic component to influence viscosity and/or fibre forming when spinning from solution may also be advantageous.

The preferred spinning material, then, is a solution or suspension which preferably comprises an organic polymer in an amount such that it is capable of forming a fibre and has cohesion properties such that the fibre form is retained during any post fibreization hardening until the fibres has hardened sufficiently not to lose its fibrous shape on detachment from a support where this is appropriate.

The additional organic component, where it is used, need be employed only in a relatively small proportion (usually within the range 0.001 to 12% and preferably 0.01 to 3%) by weight of the suspension, although the precise concentration for any particular application can easily be determined by trial.

The degree of polymerisation of the additional organic component is preferably greater than about 2000 units linearly; a wide range of such polymers is available. An important requirement is solubility of the polymer in the selected solvent or suspending medium which is preferably water. As examples of water-soluble polymeric compounds we may mentioned polyethylene oxide, polyacrylamide, polyvinyl pyrrolidone and polyvinyl alcohol; where an organic medium is employed to prepare the spinning material, either as the sole liquid solvent or as a component thereof, a further wide range of organic polymeric compounds is available, for example polystyrene and polymethylmethacrylate.

The degree of polymerisation of the polymer will be selected in the light of required solubility and the ability of the polymer to impart the desired properties of cohesion and viscosity to the fibreizable liquid.

We have found that generally the viscosity of the fibreizable liquid whether due solely to the presence of the fibreizable liquid polymer or partly contributed to by the additional organic polymer should be greater than 0.1 but not greater than 150 poise. Preferably it is between 0.5 to 50 poise and more preferably between 1 and 10 poise, (viscosities being measured at low shear rates). The viscosity required using a given additional organic polymer will vary with the molecular weight of the polymer, i.e. the lower the molecular weight the higher the final viscosity needed. Again, as the molecular weight of the polymer is increased a lower concentration of it is required to give good fibreization. Thus, as examples we would mention that in the preparation of polytetrafluoroethylene tubes we have found that using a polyethylene oxide of MW 100,000 as the additional organic polymer a concentration of about 12% by weight relative to the PTFE content is needed to give satisfactory fibreization, whereas with a MW of 300,000 a concentration of 1 to 6% may be adequate. Again, at a MW of 600,000 a concentration of 1 to 4% is satisfactory, while at a MW of 4×10^6 a concentration as low as 0.2% may give good fibreization.

The concentration of the fibreizable poly-

mer will depend upon the amount required to provide adequate fibre properties, and will be influenced also by the need to produce a liquid of appropriate viscosity and speed of fibre hardening. Thus in the case of a dispersion we may use a concentration within the range 25% w/w to saturation, (in the case of a dispersion, 'saturation' means the maximum concentration which may be included without destroying the useful spinnability of the liquid) preferably 40 to 70% and more preferably 50 to 60%, and in the case of a solution we may use a concentration within the range 10 to 60% w/w, preferably 20 to 35% w/w.

It will be appreciated that the concentration of the components must each be adjusted to take account of the presence and concentration of any other and their relative effects upon viscosity, etc.

The degree of polymerisation of the polymer will be selected in the light of required solubility and the ability of the polymer to impart the desired properties of cohesion and viscosity to the fibreizable liquid.

Any convenient method may be employed to bring the spinning material into the electrostatic field, for example we have supplied the spinning liquid to an appropriate position in the electrostatic field by feeding it to a nozzle from which it is drawn by the field, whereupon fibreization occurs. Any suitable apparatus can be employed for this purpose; thus we have fed the spinning material from a syringe reservoir to the tip of an earthed syringe needle, or plurality of needles, the tips being located at an appropriate distance from an electrostatically charged mandrel. Upon leaving the needle the material forms fibre between the needle tip and the mandrel.

The optimum distance of the nozzle from the mandrel is determined quite simply by trial and error. We have found, for example that using a potential of the order of 20 Kv a distance of 5–35 cm is suitable, but as the charge, nozzle dimensions, liquid flow rate, charged surface area etc. are varied so the optimum distance may vary, and it is most conveniently determined as described.

The prosthesis may be obtained by spinning upon a mandrel of suitable shape. Where appropriate the mandrel may be made removable from within the spun prosthesis for example by collapsing the mandrel (e.g. by using an inflatable mandrel), by dissolution (where a mandrel comprising a suitably soluble material has been used), or by melting. The mandrel may be made from any of a variety of materials. A metallic former is preferred and aluminium is particularly preferred. In particular it may be mentioned that a polyurethane tube is preferably peeled from an aluminium mandrel while an aluminium mandrel may be dissolved in sodium hydroxide solution to remove it from within a PTFE tube. To facilitate peeling a polyurethane tube from an aluminium mandrel, the latter may be conveniently covered with a layer of flexible polyurethane foam.

The electrostatic potential employed will usually be within the range 5 Kv to 1000 Kv, conveniently 10–100 Kv and preferably 10–50 Kv.

The prosthesis may be of any of a variety of shapes, appropriate to its intended function. Thus it may for example be, as already described, a simple straight tube, or it may be bent or curved, it may form a loop, or an anastomosis, or it may bifurcate. In all such cases, however, at least a portion of the prosthesis will be in the form of a tube having the dimension set out above.

The thickness of the wall of the prosthesis may vary within wide limits, and will be influenced inter alia by the strength and/or elasticity which is desired in the product. Again the thickness may be different in different parts of the prosthesis. However, we prefer that a substantial portion of the wall should be of the thickness of the order of 0.5 to 5 mm, more preferably 1 to 3 mm.

The actual dimension of the prosthesis will, of course, be selected in the light of its intended function and location, and of course they may be prepared upon a mandrel of corresponding dimensions and configuration.

The use of fibres of small diameter, e.g. 0.1 to 10 micron and particularly 0.4 to 10 micron is preferred and preferably at least the part of the prosthesis adjacent the bore will be porous, preferably having the majority of pores of the order of 5 to 25, preferably 7 to 15 microns in diameter.

The preferred prostheses comprise fibres of an appropriate polyurethane selected from the wide range of materials available on the basis of ease of fabrication, lack of toxicity, solubility, mechanical properties, degree of biodegradability, etc. While it is preferred that a completely polymerised polyurethane dissolved in a suitable solvent (together with other additives as required) is used as the spinning solution we do not exclude the possibility of spinning incompletely polymerised polyurethane, completion of polymerisation being effected during or after spinning. Thus for example it is possible to spin an incompletely polymerised polyurethane product onto an inflatable mandrel in one configuration, inflate the mandrel to stretch the formed product, for example to increase its porosity to a desired degree, and then to cure the product in its expanded condition.

Products having different properties may be obtained by adjusting their composition, for example by spinning a liquid containing a plurality of components, each of which may contribute a desired characteristic to the finished product, or by simultaneously spinning from different liquid sources fibres of different composition which are simultaneously deposited to form a layer having an intimately intermin-

gled mass of fibres of different material. A further method is to produce a product having a plurality of layers of different fibres (or fibres of the same material but with different characteristics e.g. diameter) deposited, say, by varying with time the fibres being deposed upon the receiving surface. One way of effecting such a variation, for example, would be to have a moving mandrel passing in succession sets of spinnerets from which fibres are being electrostatically spun, said fibres being deposited in succession as the receiver reaches an appropriate location relative to the spinnerets.

To allow high production rates, hardening of the fibres should occur rapidly and this is facilitated by the use of concentrated fibreizing liquids (so that the minimum liquid has to be removed), easily volatile solvents (for example the liquid may be wholly or partly of low boiling organic liquid) and relatively high temperatures in the vicinity of the fibre formation. The use of a gaseous, usually air, blast, particularly if the gas is warm, will often accelerate hardening of the fibre. Careful direction of the air blast may also be used to cause the fibres, after detachment, to lay in a desired position or direction.

The following example illustrates the invention:—

EXAMPLE 1

The preparation of a prosthesis is illustrated in the figure. A mandrel in the form of an axially rotating aluminium tube of 1.5 cm diameter (10) was charged to 50 Kv and a 12% solution of polyurethane ("Daltermold" 338E) in dimethyl formamide was electrostatically spun on to the tube through a bank of 24 needles (one only shown, for clarity) at the rate of 1 gm/needle/hour. The tube (11) produced has a wall thickness of 2 mm consisting in the main of 0.5 μ diameter fibres bonded where they are contacted.

The tube was implanted by suturing into the descending aorta of a pig. After 6 months the graft was examined and showed a well attached thin intina, intramural capillary growth and a firmly attached adventitial layer. There was no thrombosis.

WHAT WE CLAIM IS:—

1. A vascular prosthesis comprising fibres prepared by electrostatically spinning an organic material and formed into a tube by collecting the spun fibres on a suitably shaped mandrel, the prosthesis comprising a tubular portion having a bore of maximum internal cross-sectional dimension up to 3 cm.

2. A vascular prosthesis according to claim 1 having a bore of maximum internal cross-sectional dimension of 0.3 to 3 cm.

3. A vascular prosthesis according to claim 1 or 2 in which the fibres comprise a polyurethane.

4. A prosthesis according to claim 1, 2 or 3 in which the fibres are of diameter 0.1 μ to 10 μ.

5. A prosthesis according to any one of the preceding claims in a configuration shape which is not a straight line.

6. A prosthesis according to claim 5 in the form of a loop, an anastomosis or bifurcation.

7. A prosthesis according to any one of the preceding claims, a substantial portion of the wall having a thickness of 0.5 to 5 mm.

8. A prosthesis according to any one of the preceding claims comprising reinforcement not formed by electrostatic spinning.

9. A prosthesis substantially as hereinbefore described.

10. A method of preparing a vascular prosthesis as claimed in claim 1 comprising the step of electrostatically spinning a fibre forming composition, and forming a tube by collecting the fibres so formed onto a suitably shaped mandrel.

11. A method according to claim 10 in which the composition is a polyurethane.

12. A method of preparing a vascular prosthesis as claimed in claim 1 and substantially as hereinbefore described.

B.J. BATE
AGENT FOR THE APPLICANTS

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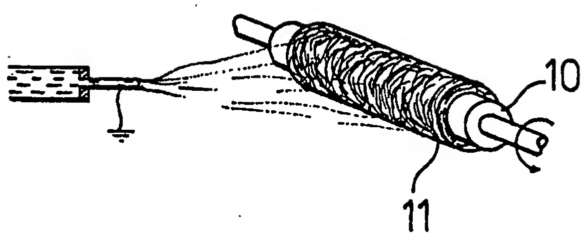
1577221 COMPLETE SPECIFICATION

1 SHEET *This drawing is a reproduction of the Original on a reduced scale*



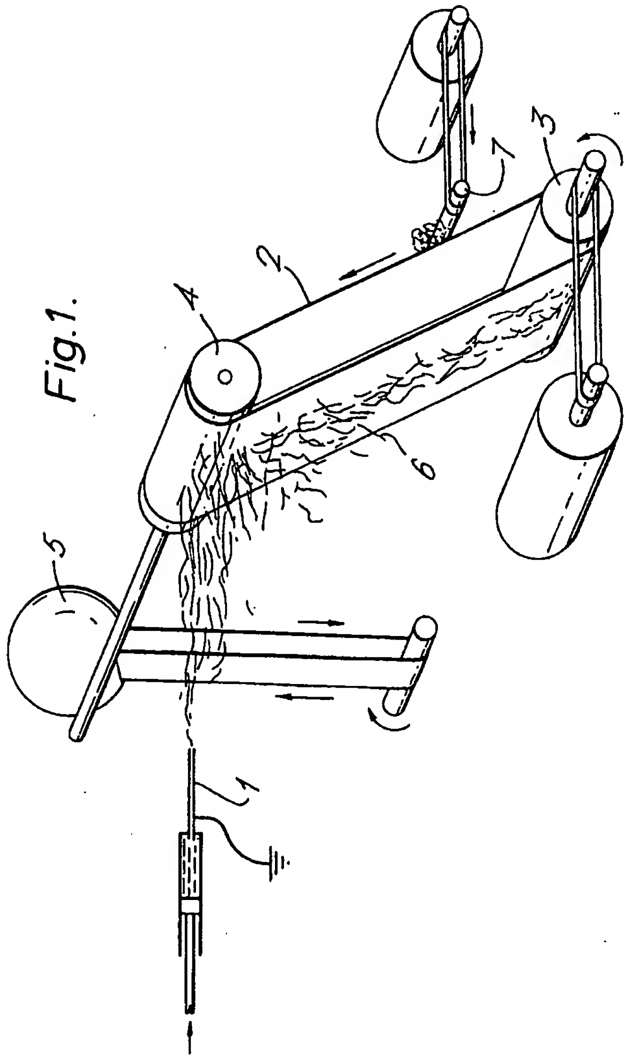


Fig.1.

1577221 PROVISIONAL SPECIFICATION

2 SHEETS *This drawing is a reproduction of the Original on a reduced scale*

Sheet 2

Fig. 2.

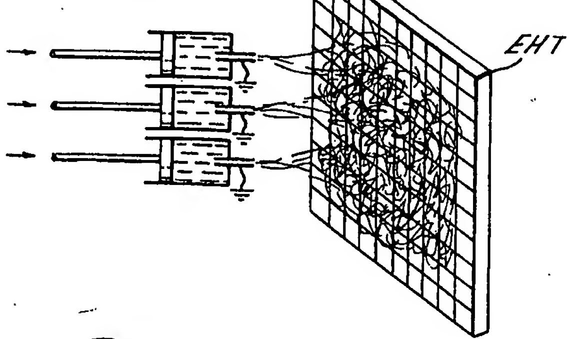


Fig. 3.

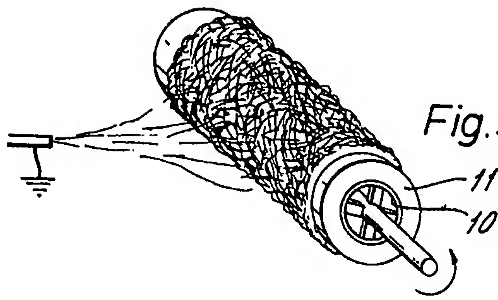


Fig. 4.